EXHIBIT A

Cancer Research

[*Cancer Research* 62, 6108-6115, November 1, 2002]

Experimental Therapeutics

MS-27-275, an Inhibitor of Histone Deacetylase, Has Marked *in Vitro* and *in Vivo* Antitumor Activity against Pediatric Solid Tumors

Jerry Jaboin[1,2], Jason Wild[1], Habib Hamidi[1], Chand Khanna, Chong Jai Kim, Robert Robey, Susan E. Bates and Carol J. Thiele[3]

Cell and Molecular Biology Section, Pediatric Oncology Branch [J. J., J. W., H. H., C. K., C. J. T.] and the Experimental Therapeutics Branch [R. R., S. E. B.], Center for Cancer Research, National Cancer Institute, Bethesda, Maryland 20892, and Department of Pathology, Seoul National University of Medicine, Seoul, Korea 100-799 [C. J. K.]

The antitumor efficacy of the synthetic benzamide derivative MS-27-275 (MS-275), an inhibitor of histone deacetylation [T. Suzuki *et al.*, J. Med. Chem., *42:* 3001–3003, 1999], was evaluated in a series of pediatric solid tumor cell lines, including neuroblastoma, rhabdomyosarcoma, Ewing's sarcoma (EWS), retinoblastoma, medulloblastoma, undifferentiated sarcoma (US), osteosarcoma, and malignant rhabdoid tumors. Treatment with MS-275 results in an increase in acetylation of histones within 4 h of drug exposure. The cell lines were treated with various concentrations of MS-275 for 3 days and incubated with [^{3}H]thymidine for 20 h before cell harvest. MS-275 inhibited [^{3}H]thymidine uptake in a dose-dependent manner in all tumor cell lines examined. The IC_{50} ranged from 50 nm in the D283 medulloblastoma cell line to 1.3 μM in the US. A common feature of MS-275 treatment of pediatric tumor cell lines was induction of p21mRNA. However, the effects on cell cycle were diverse because in some cases MS-275 induced an increase in G_1 or G_2, whereas in others, there was an induction of apoptosis. In EWS, the EWS/fli chimeric transcription factor created by the t(11;22) suppresses transforming growth factor (TGF) ßRII transcription, however, MS-275 was able to induce an increase in TGF-ßRII mRNA and restore TGF-ß signaling. Using xenograft orthotopic models of US, EWS, and neuroblastoma, we find that the growth of established tumors is inhibited in mice treated with MS-275.